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Neuro-genetics of persistent pain

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Pain is a complex consciousness that emerges from the brain, and is commonly a result of nociception; the physiological process initiated by activation of specialised high-threshold peripheral sensory neurons. When pain is persistent, its affective aspects can dominate and cause considerable suffering. This chronic pain state is not an inevitable consequence of physical injury or disease. Instead, susceptibility to chronic pain results from complex interactions between multiple genes and the environment that influence nociception and regulate the consciousness of pain. The biological bases for chronic pain can now be defined and measured by brain neuroimaging at a systems level, where penetrance of genetic variation should be higher when compared to syndromal phenotypes. To date, very few neuroimaging studies have attempted to connect brain activity associated with pain to genes. We review these together with other pertinent studies here, and suggest how neuroimaging endophenotypes might prove useful for the development of treatments for chronic pain.

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Introduction

Pain is the unpleasant consciousness that we associate with, or describe in terms of, a bodily injury [1]. It serves a useful protective purpose and normally confers a survival advantage. Clinicians have long regarded pain as a symptom or warning of disease that should be investigated as such in order to allow timely treatment of pathology. Unfortunately, medicine does not yet possess every cure, or indeed knowledge of all pathophysiology that can cause pain. Pain can persist despite the best efforts of physicians, and chronic pain may be defined based on duration, but is in reality a suffering strongly associated with feelings of anxiety, depression and despair [2]. Approximately 20% of the adult population in the Western world report living with chronic pain [3], which consequently incurs appreciable health-care and socio-economic costs [4] in addition to the increasing burden of suffering by members of our society.

The chronic pain state is *not an inevitable consequence* of physical injury or disease. Traumatic or infectious injury to soft tissues can cause pain. However, most individuals experiencing these insults do not develop chronic pain [5]. Susceptibility to persistent pain is believed to result from complex interactions between multiple genes and the environment. However, identifying genes with significant or reproducible effect size, even in large-scale genetic association studies, has proven difficult [6]. Part of that difficulty stems from diagnostic imprecision. Clinical pain syndromes are currently diagnosed based on observed behaviour or self-report. To date, there are no pathognominic features or biomarkers that distinguish between most pain syndromes, with the exception of inherited erythromelalgia, a Mendelian genetic disorder associated with gain-of-function mutations in the SCN9A gene [7].

Preclinical approach to pain genetics

Candidate genes associated with chronic pain states can be identified in other species, where biological mechanisms underlying a specific behaviour reflecting pain in humans can be investigated more invasively. The discovery of GCH1 functional polymorphisms for persistent pain is an elegant example [8]. Most pre-clinical genetic studies have focussed on nociception, the physiological process initiated by activation of specialised high-threshold sensory neurons [9]. These noxious stimulus detectors, or nociceptors, are evolved to trigger protective reflexes, which are undoubtedly essentially for survival. Neuroplasticity in the nociceptive system has been shown to drive abnormal reflexes and behaviours in animal models of clinical pain [10]. However, animal models may not capture adequately crucial aspects of chronic pain in humans [11], and those that capture features are difficult to measure based upon animal behaviour [12,13]. Furthermore, translation of genetic data from one rodent species to humans may be undermined by our current inability to extrapolate from one rodent to another [14]: a recent meta-analysis of microarray (gene expression profiling) studies of chronic pain suggests that almost no genes in the dorsal root ganglia that were consistently upregulated or downregulated by nerve or inflammatory injury in the rat could be confirmed as similarly regulated by those injuries in the mouse [15]. Finally, the more invasive methods employed in animal

studies may not lend themselves well to studies of pain neurobiology in humans, limiting perhaps translation of pre-clinical science.

Human brain neuroimaging and the genetics of pain

Hippocrates, in the fifth century B.C., asserted that 'Men ought to know that from the brain, and from the brain alone, arise our sorrows, *pain*, grief, and tears — these things that we suffer all come from the brain' [16]. Robust scientific evidence for that philosophical intuition for pain has only been made available through the advent of brain neuroimaging research in the late 20th century [17]. Widespread activity in the brain during pain is now consistently recorded and reinforces the view of pain as a complex multi-dimensional experience with sensory and affective components [18]. Brain neuroimaging can quantify neural structure and function associated with pain on a systems level, providing biological phenotypes that are closer to the neurobiology of genetic function compared to syndromal phenotypes [19]. Consequently, penetrance of genetic variation on neuroimaging phenotypes should be higher, which ought to make finding genes that impact on the pain phenotype more likely. The earliest demonstrations of neuroimaging endophenotypes come from psychiatric neuroscience, because the need for biological bases is well recognised in that clinical discipline [20••].

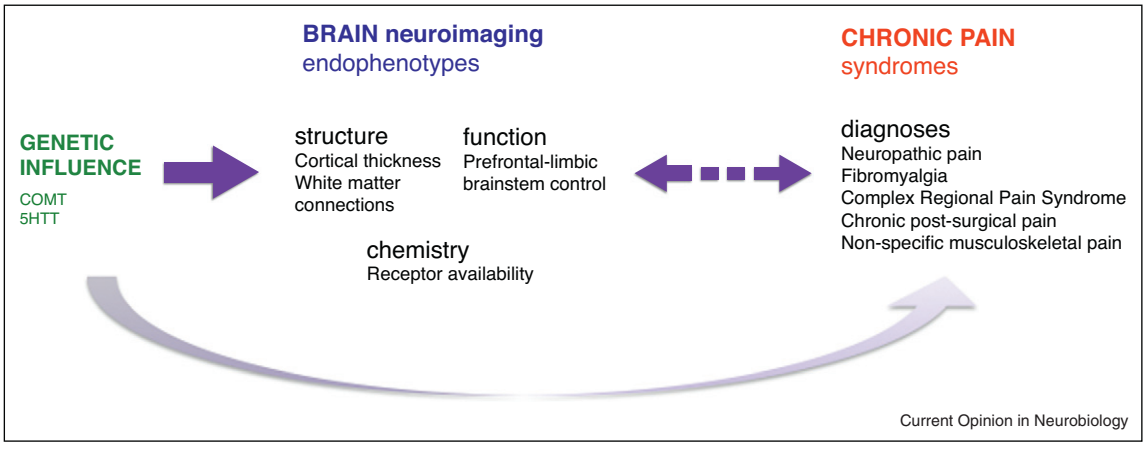
The latest non-invasive brain neuroimaging techniques that are already being used to define potential endophenotypes for chronic pain have been reviewed recently [21••]. To date, very few neuroimaging studies have attempted to connect brain activity associated with pain to genes. The published studies have focused on functional genetic polymorphisms that influence catecholamine and serotonergic neurotransmission. We review these together with other pertinent studies, and suggest where brain imaging and genetics might prove useful for the development of treatments for chronic pain (Figure 1).

Catechol-O-methyltransferase (COMT) genetics and pain neuroimaging

Catechol-O-methyltransferase (COMT) is an enzyme that is involved in the degradation of catecholamine neurotransmitters (including dopamine, noradrenaline and adrenaline) after their release in the synaptic cleft, and regulates a number of neurophysiological functions. A single nucleotide polymorphism associated with a valine to methionine substitution leads to a 38% decrease in enzyme activity in Met^{158}-homozygotes compared with Val^{158}-homozygotes, with the Val^{158}/Met^{158}-heterozygotes demonstrating intermediate activity [22].

Zubieta and colleagues [23] first demonstrated the relevance of COMT Val158Met polymorphism on pain and endogenous opioidergic transmission. Using positron emission tomography (PET) with the μ-opioid receptor-selective radiotracer [^{11}C] carfentanil, they found that Met^{158}-homozygotes showed diminished regional opioidergic responses to a tonic sustained noxious stimulus, as well as increased ratings of pain compared with Val^{158}/Met^{158}-heterozygotes. The opposite was found for Val^{158}-homozygotes. More recently, two independent groups have attempted to distinguish COMT polymorphisms in individuals using functional magnetic resonance imaging (fMRI) to map brain responses to brief noxious heat stimuli [24,25•]. In contrast to the study of sustained pain by Zubieta and colleagues, neither group of investigators detected a significant effect of genotype on subjective ratings of more phasic pain. The fMRI studies did demonstrate increased brain activation in Met^{158}-homozygotes,

Figure 1



Genetics are weakly linked to the development of chronic pain, but can influence neuroimaging-based indices of brain structure, neurochemistry and function. These measurable indices can provide endophenotypes for chronic pain syndromes, on which small genetic effects are likely to be more apparent.